

Finding Functional Modules within Metabolic Networks

Marko Budinich, Jérémie Bourdon & Damien Eveillard



Context of Metabolic Modeling in Systems Biology

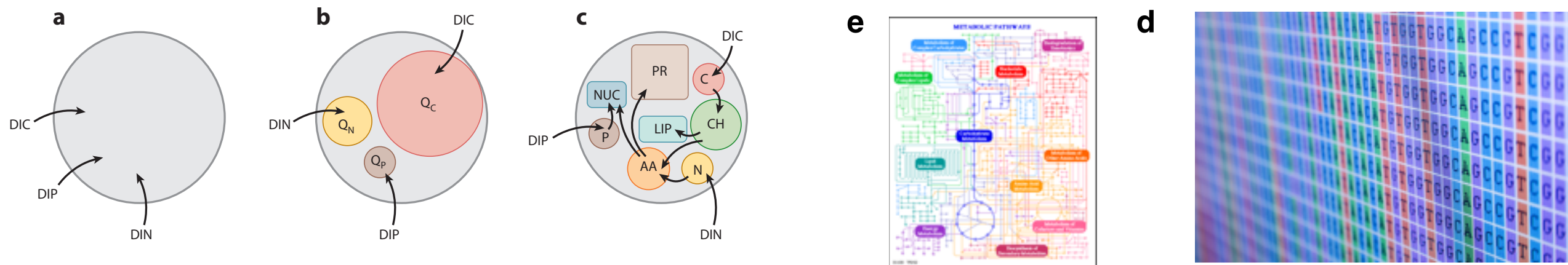


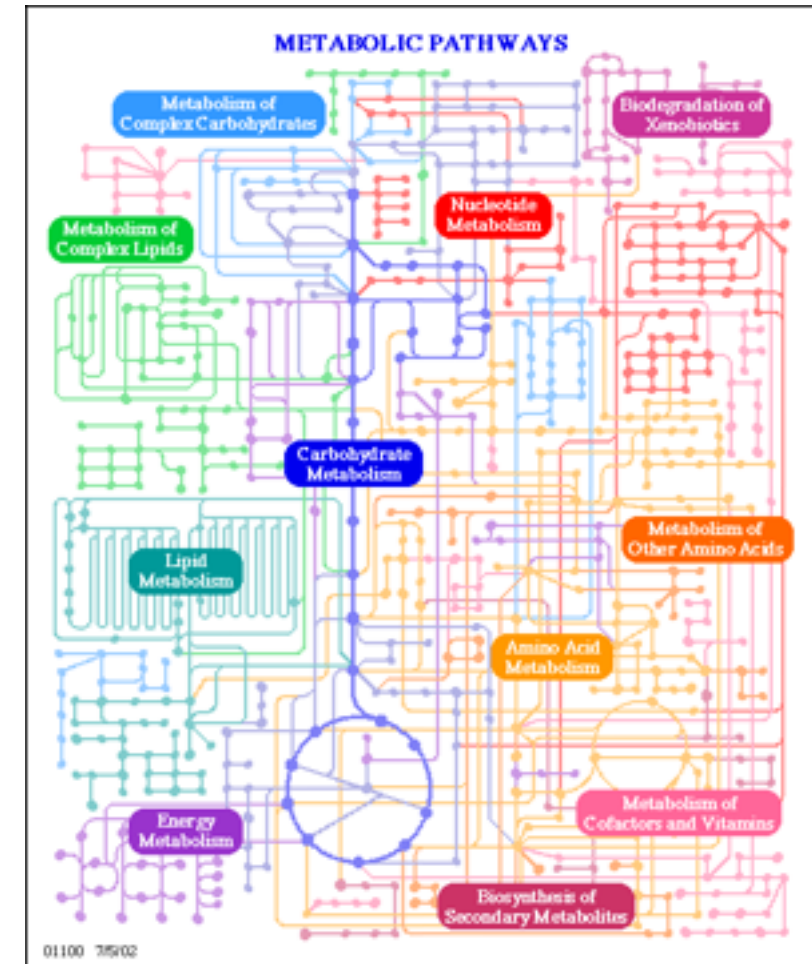
Figure 13
Schematic representation of the parameterization of photoautotroph physiology employed in marine ecosystem models: (a) Monod-type, (b) Droop/Caperon-type with individual quota for each element, carbon (Q_C), nitrogen (Q_N), and phosphorus (Q_P), (c) schematic concept for a model of algal physiology that resolves key biochemical components of an algal cell, including carbohydrates (CH), lipids (LIP), amino acids (AA), nucleic acids (NUC), and proteins (PR). Abbreviations: DIC, dissolved inorganic carbon; DIN, dissolved inorganic nitrogen; DIP, dissolved inorganic phosphorus. Figure inspired by Reynolds (2006), Pahlow & Oschlies (2009), Klausmeier et al. (2004), Shuter (1979), and others.

Physiology ++

Functional Genomic

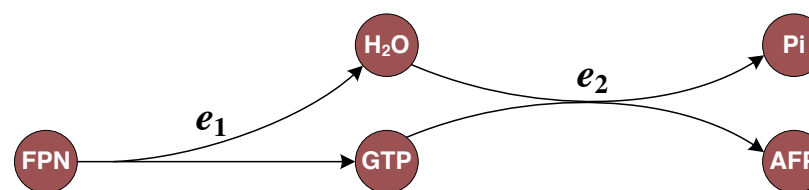
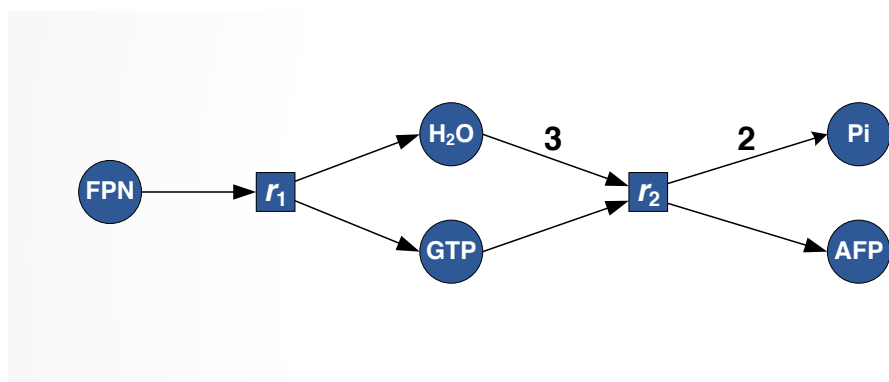
Follows MJ, Dutkiewicz S (2011). Modeling diverse communities of marine microbes. *Ann Rev Mar Sci* 3: 427–451.

Metabolic Network Definition



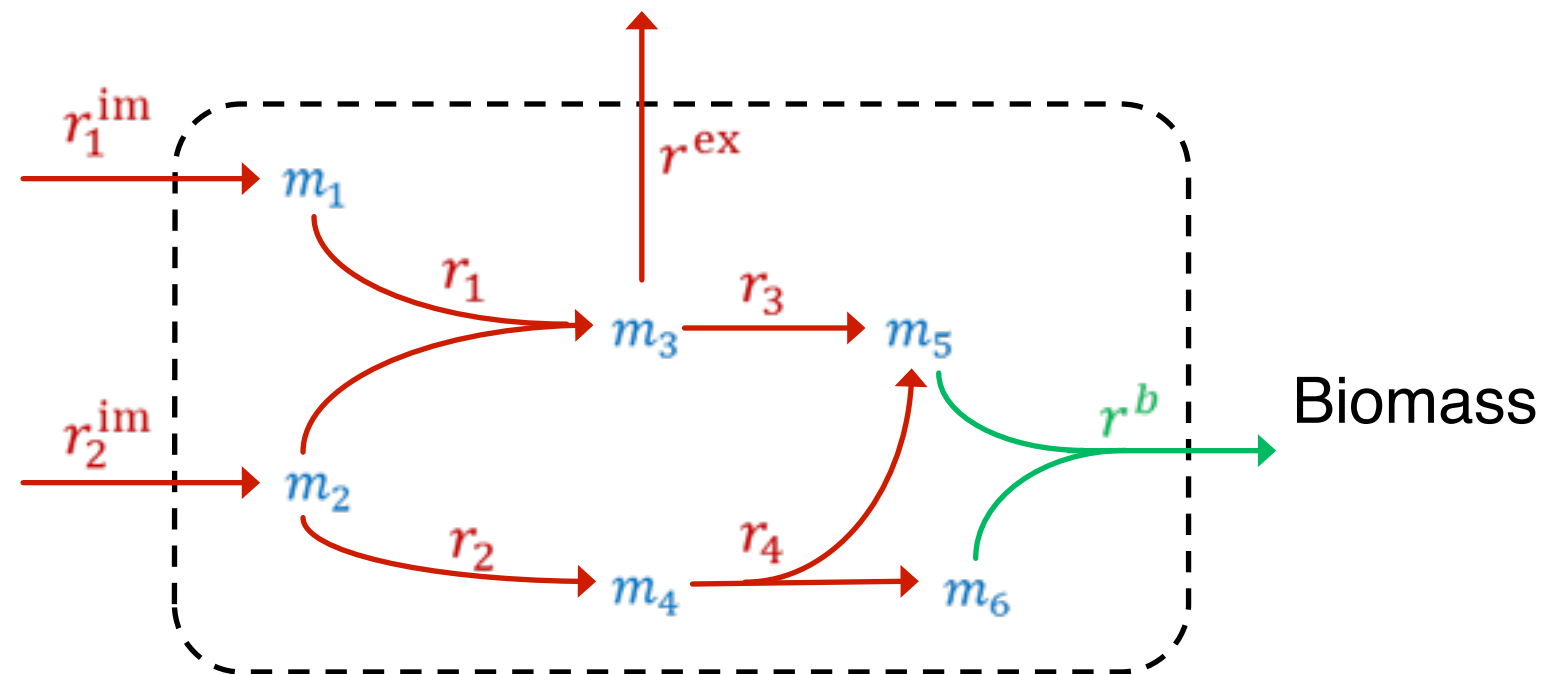
- Structure and function

- Chemical reactions of a cell/organism
- Conversion of nutrients into cellular biomass and energy
- Represented as bipartite graph, hypergraph, or stoichiometric matrix



$$\begin{array}{c}
 \text{FPN} \\
 \text{H}_2\text{O} \\
 \text{GTP} \\
 \text{P}_1 \\
 \text{AFP}
 \end{array}
 \begin{pmatrix}
 r_1 & r_2 \\
 -1 & 0 \\
 1 & -3 \\
 1 & -1 \\
 0 & 2 \\
 0 & 1
 \end{pmatrix}$$

Metabolic Network Definition



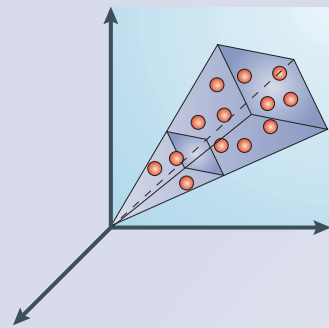
Linear program (FBA)

$$S = \begin{matrix} & r_1 & r_2 & r_3 & r_4 & r_1^{im} & r_2^{im} & r^{ex} & r^b \\ \begin{matrix} m_1 \\ m_2 \\ m_3 \\ m_4 \\ m_5 \\ m_6 \end{matrix} & \begin{pmatrix} -1 & 0 & 0 & 0 & 1 & 0 & 0 & 0 \\ -1 & -1 & 0 & 0 & 0 & 1 & 0 & 0 \\ 1 & 0 & -1 & 0 & 0 & 0 & -1 & 0 \\ 0 & 1 & 0 & -1 & 0 & 0 & 0 & 0 \\ 0 & 0 & 1 & 1 & 0 & 0 & 0 & -1 \\ 0 & 0 & 0 & 1 & 0 & 0 & 0 & -1 \end{pmatrix} \end{matrix} \quad v = \begin{pmatrix} v_1 \\ v_2 \\ v_3 \\ v_4 \\ v_1^{im} \\ v_2^{im} \\ v^{ex} \\ v_b \end{pmatrix}$$

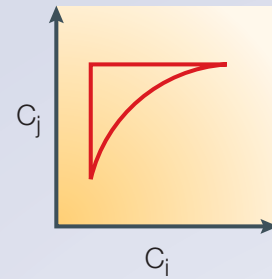
$$\begin{aligned} \max \quad & v_b \\ \text{s.t.} \quad & Sv = 0 \quad (1) \\ & v_{min} \leq v \leq v_{max} \quad (2) \end{aligned}$$

Flux Balance Analysis

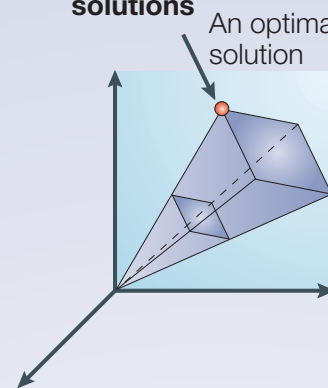
15 Sampling



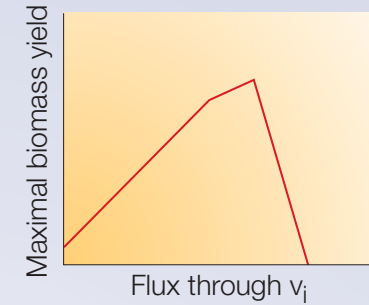
16 Bi-linear concentration cone



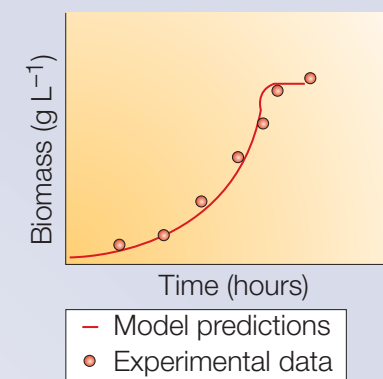
1 Identifying optimal solutions



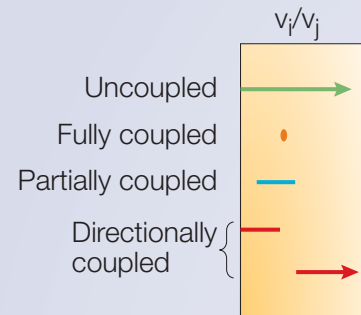
2 Robustness



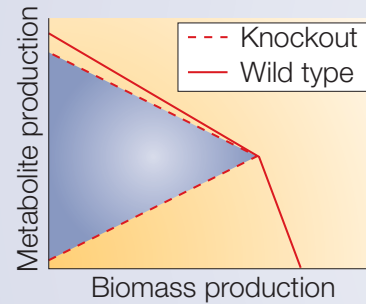
3 Dynamic simulations



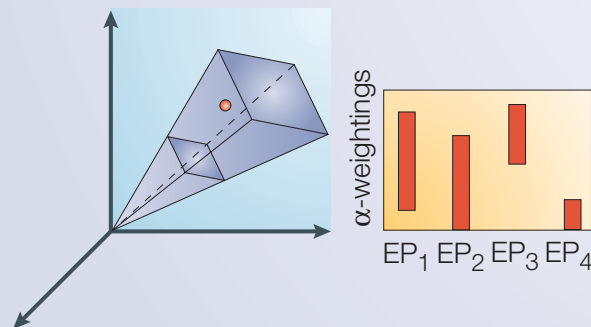
14 Flux coupling



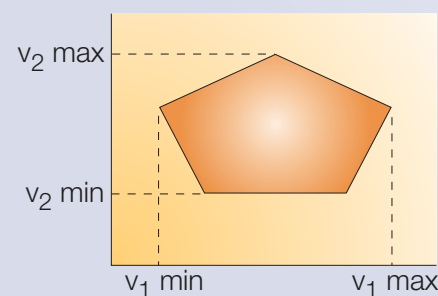
13 OptKnock



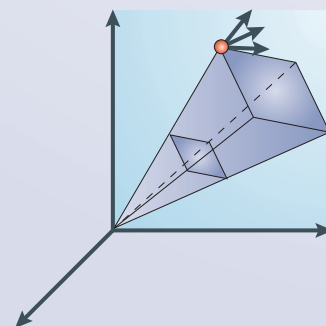
12 α -spectrum



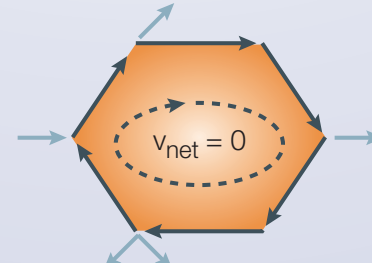
11 Flux variability



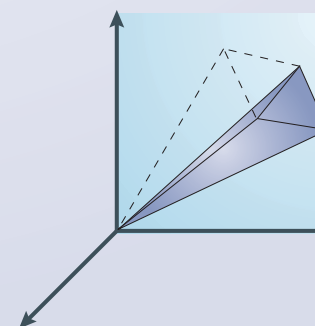
10 Finding objective functions



9 Energy balance analysis

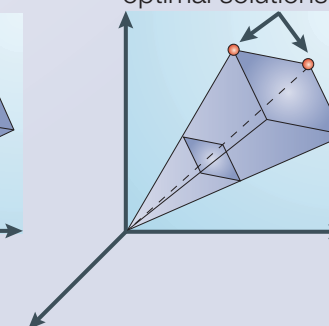


8 Regulatory constraints

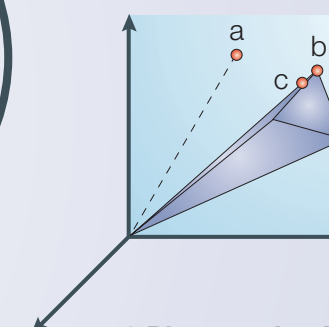


7 Alternate optima

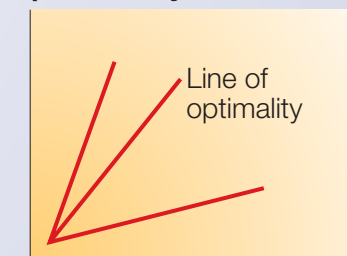
Equivalent optimal solutions



5 Gene deletions

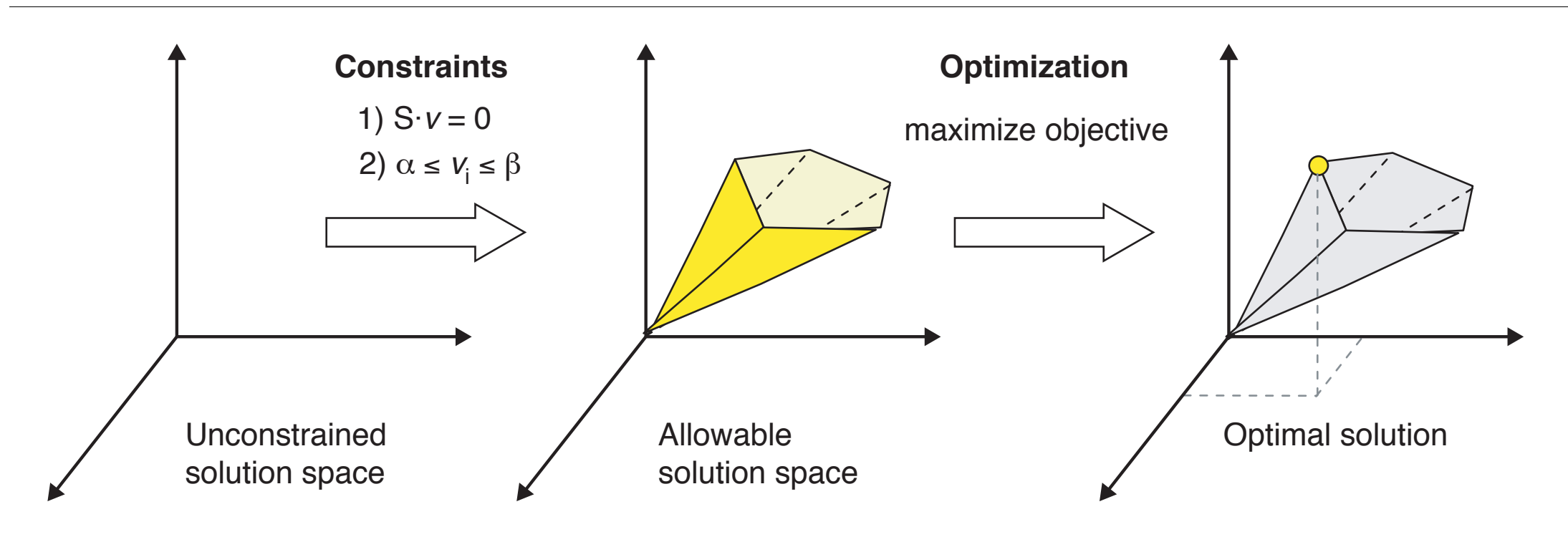


6 Phenotypic phase plane analysis



Price, et. al, Nature Review, 2004

FBA extensions



$$\text{opt} := \max\{v_{\text{Biomass}} : S v = 0, \quad l \leq v \leq u\}$$

- Great interest to study dependencies between fluxes through pair of reactions:
- But remains complicated to investigate genome-wide models
- One optimal solution is not realistic

Decomposing the solution space is hard

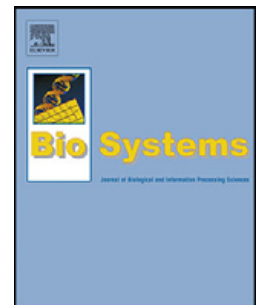
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A note on the complexity of finding and enumerating elementary modes

Vicente Acuña^{a,b,*}, Alberto Marchetti-Spaccamela^c, Marie-France Sagot^{a,b}, Leen Stougie^{d,e}

^a Université de Lyon, F-69000 Lyon; Université Lyon 1; CNRS, UMR5558, Laboratoire de Biométrie et Biologie Evolutive, F-69622 Villeurbanne, France

^b INRIA Rhône-Alpes, 655 avenue de l'Europe, 38330 Montbonnot Saint-Martin, France

^c Università di Roma "La Sapienza", Via Eudossiana 18, 00184 Rome, Italy

^d Vrije Universiteit Amsterdam, De Boelelaan 1105, 1081HV Amsterdam, The Netherlands

^e Centrum voor Wiskunde en Informatica, Kruislaan 413, 1098SJ Amsterdam, The Netherlands

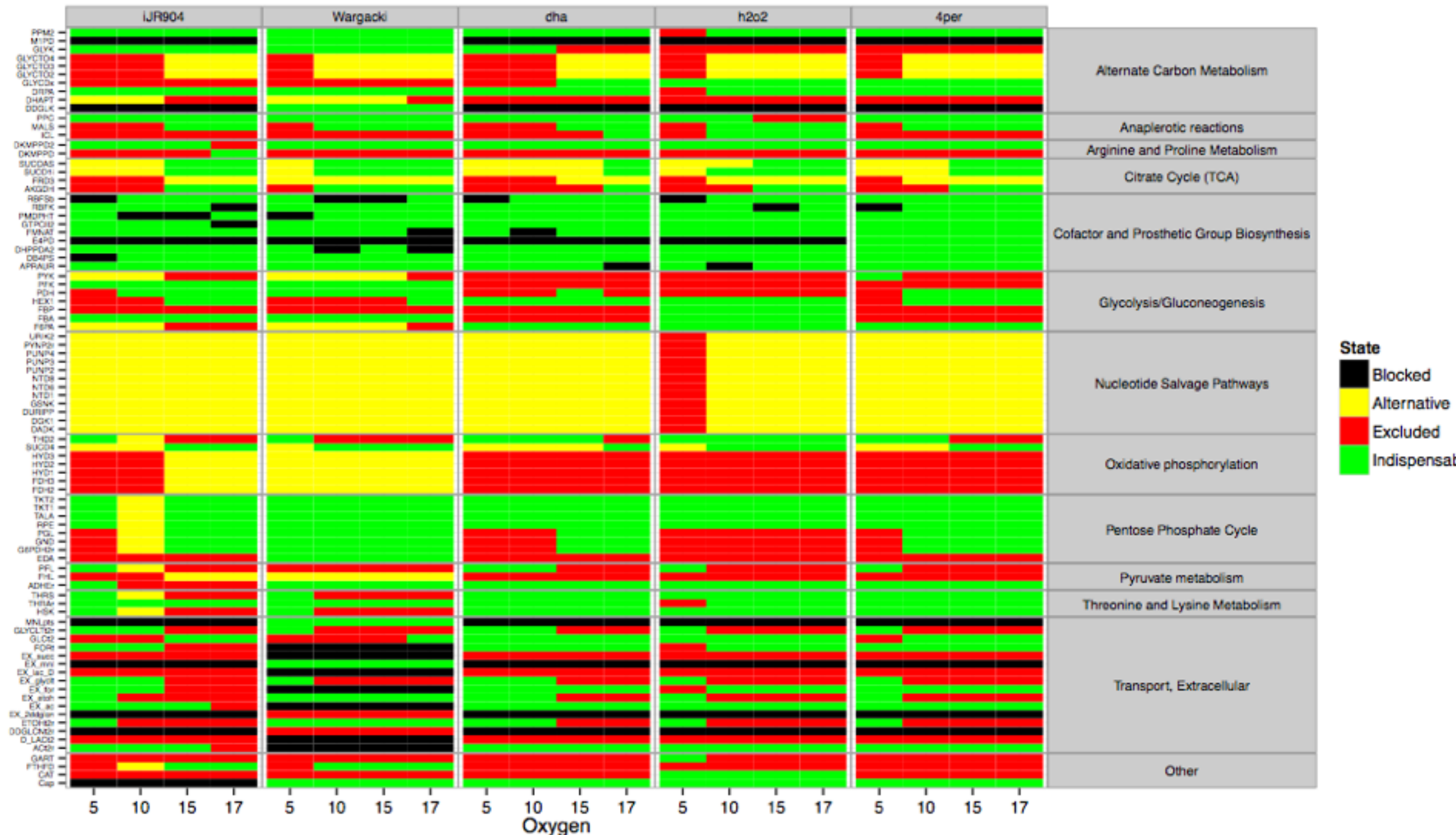
FVA insights

- Deeper analysis that study all the flux realizing the optimal objective
- Not a single optimal flux vector, but set of optimal solutions : optimal flux space

$$P_{opt} := \max\{v : Sv = 0, \quad l \leq v \leq u, v_{\text{Biomass}} = \text{opt}\}$$

Flux Variability

- For a given objective (e.g. biomass production), upper and lower bounds of all steady state reaction fluxes can be determined



Deeper analysis of Optimal Flux Space

$$P_{opt} := \max\{v : Sv = 0, \quad l \leq v \leq u, v_{\text{Biomass}} = \text{opt}\}$$

- This space is similar to the feasible flux space:
 - Vertices: optimal pathways
 - Linealities: reversible cycles
 - Rays: irreversible cycles

Application of «standard » polyhedra description, but focused on Optimal Flux Space

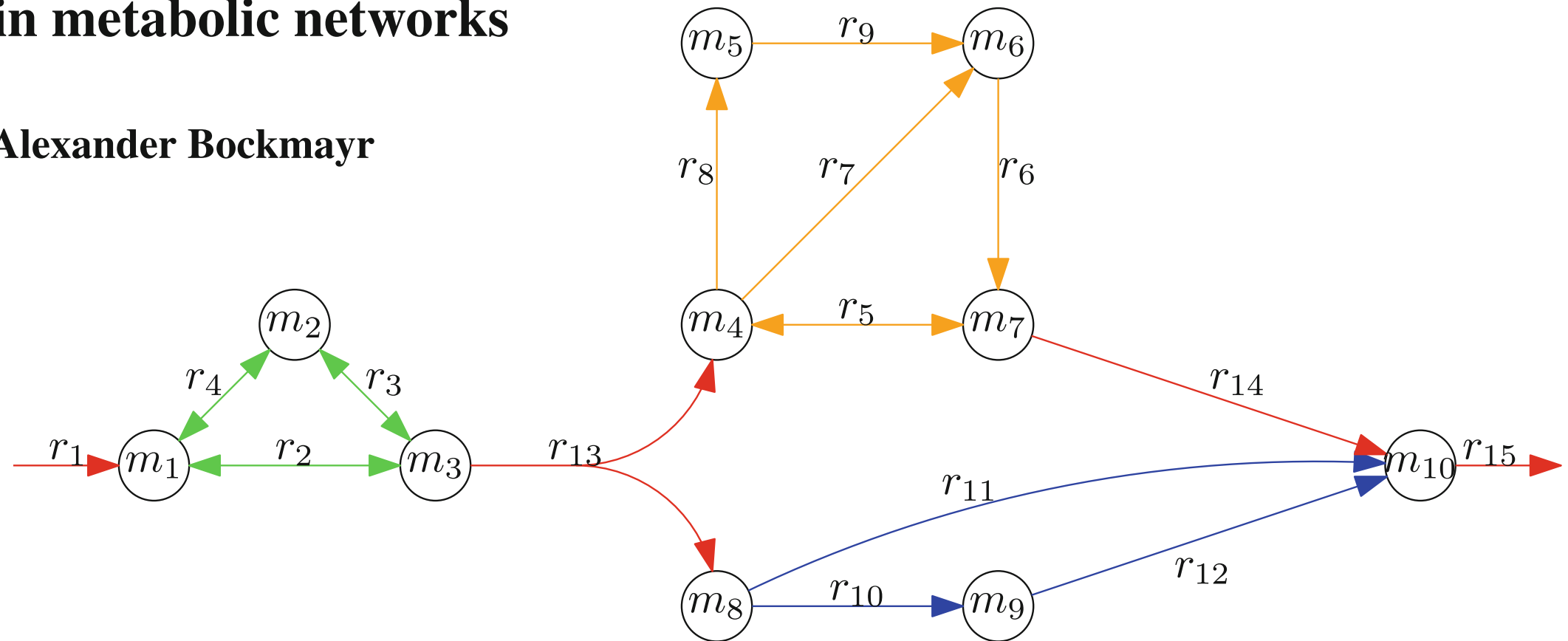
Deeper analysis of Optimal Flux Space

Within this space, correlated reactions are grouped into flux modules

Flux modules decompose the network and provide an comprehensive understanding of the whole flux space

Flux modules in metabolic networks

Arne C. Müller · Alexander Bockmayr



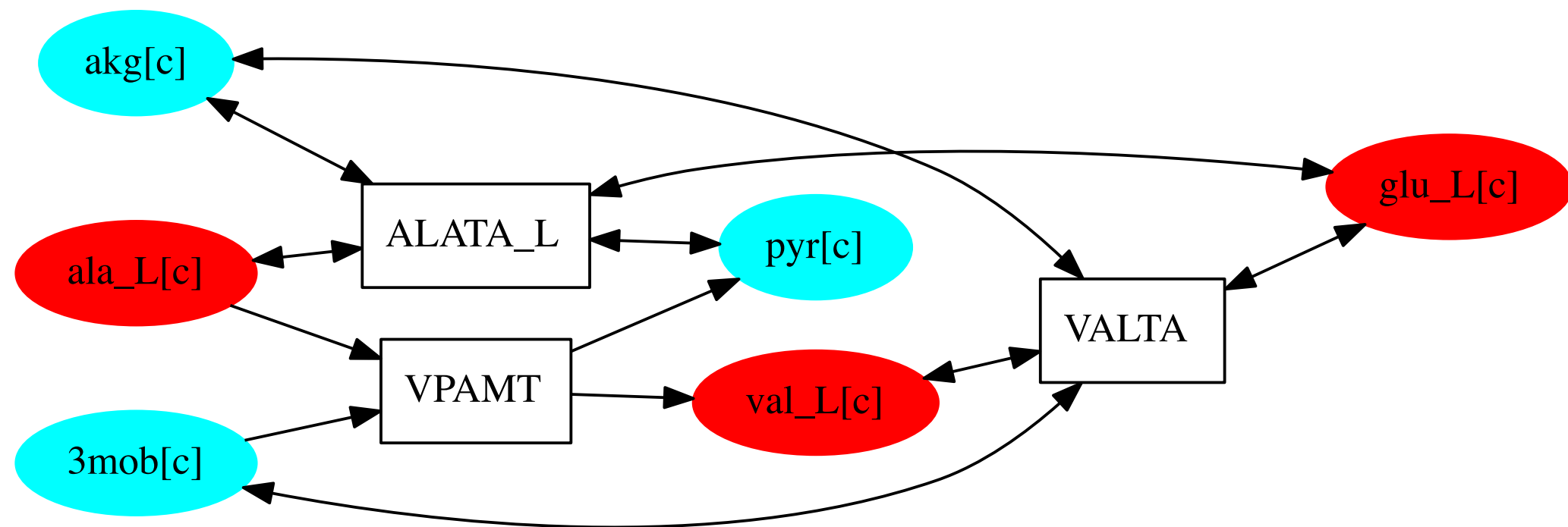
- One assumes the flux in **r1** as fixed to 1
- Then fluxes on **r13**, **r14** and **r15** are fixed
- $\{r2, r4, r3\}$ $\{r5, r6, r7, r8, r9\}$ and $\{r10, r11, r12\}$ are modules

Application on E. coli

Using iAF1290 model, one calculates modules when the bacteria grows on glucose and aerobic condition

Modules	Number of Rxns	Description
Not in module	2290	-
Module MO1	38	Nucleotide Salvage Pathways
Module MO2	3	Membrane Lipid Metabolism
Module MO3	12	Membrane Transport
Module MO4	3	Alanine, Aspartate , Valine, Leucine and
Module MO5	14	Respiration / Electron transfer reactions
Module MO6	5	Glycolysis/ gluconeogenesis
Module MO7	3	Cofactor and Prosthetic Group Biosynthesis
Module MO8	11	Exchange reactions
Module MO9	2	Glucose Intake

Illustration on Module MO4

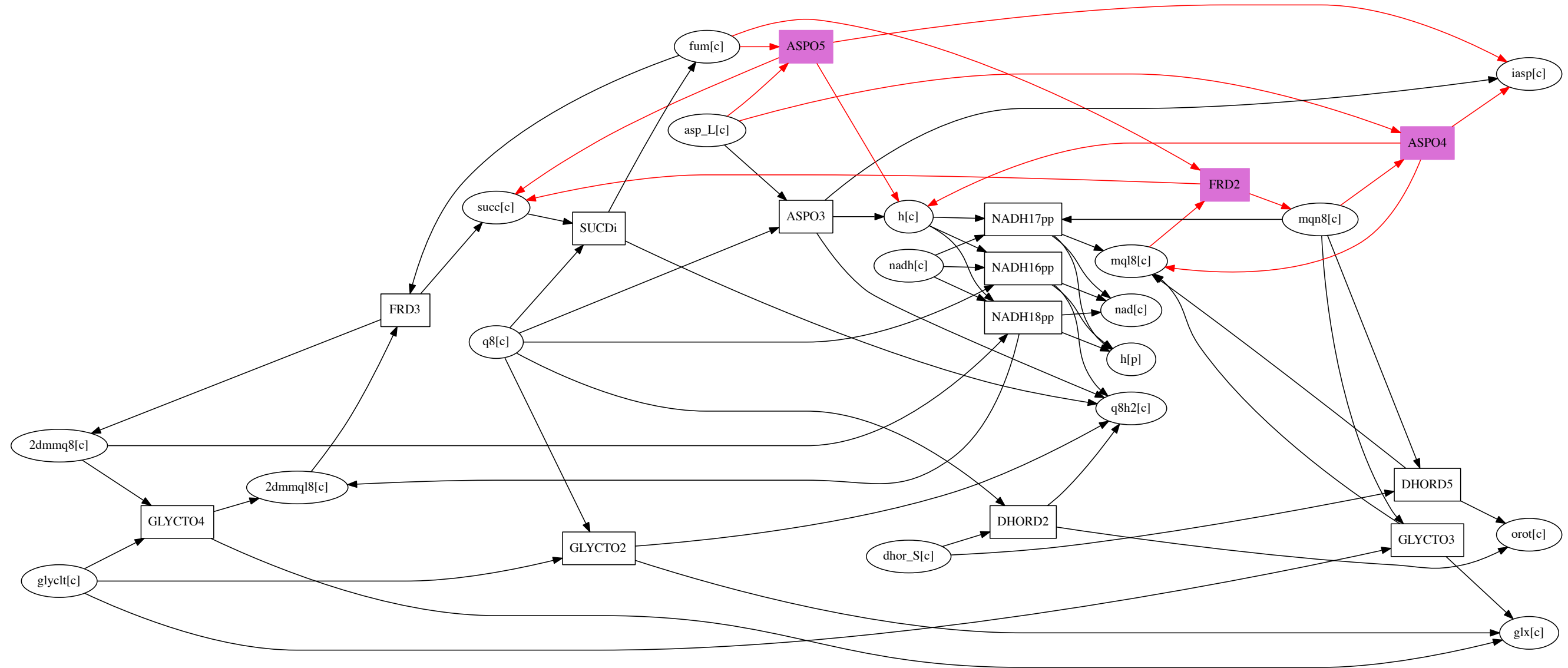


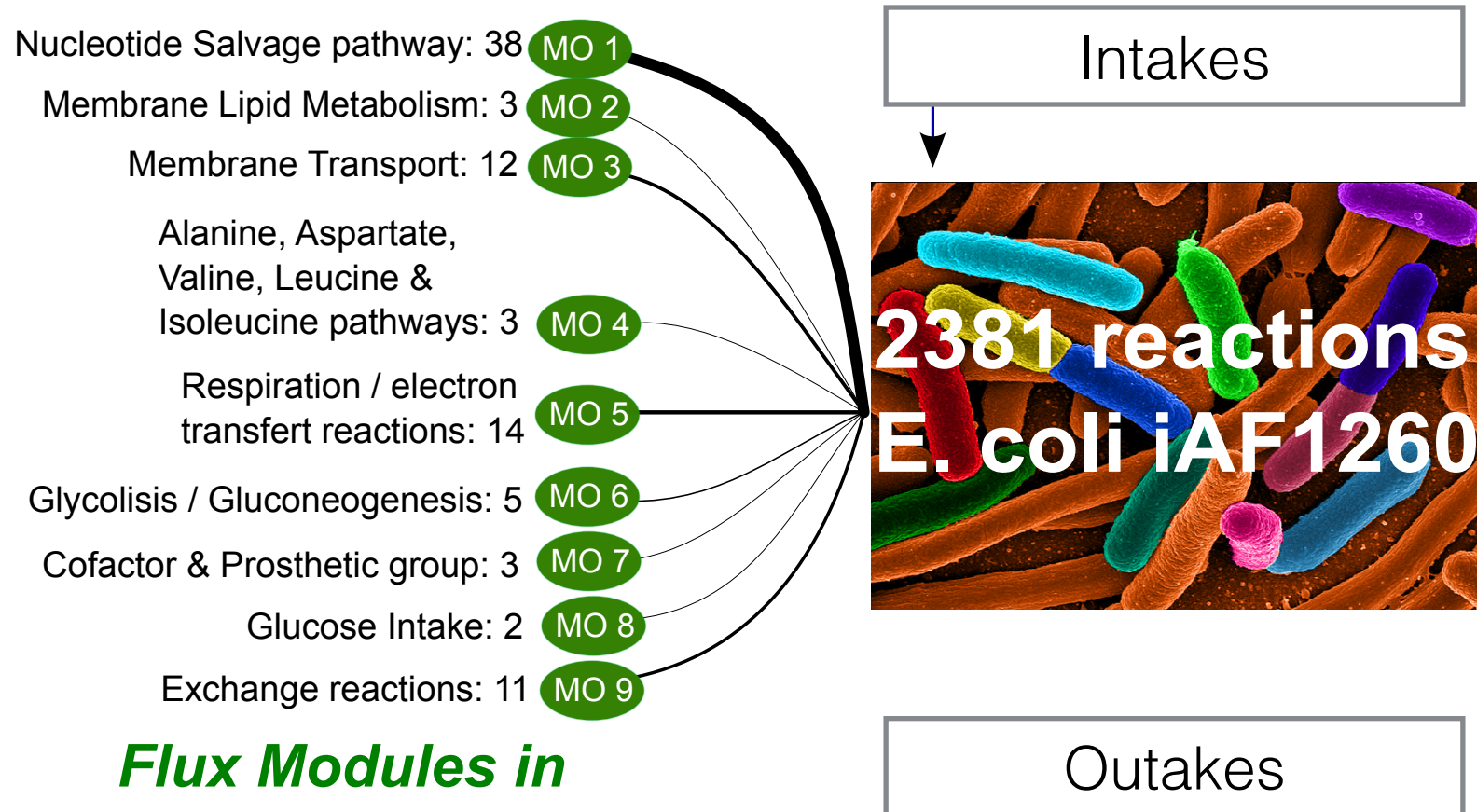
Reactions (boxes) and metabolites (ellipses) respectively cyan and red for amino acids and carbohydrates

Application on E. coli (2)

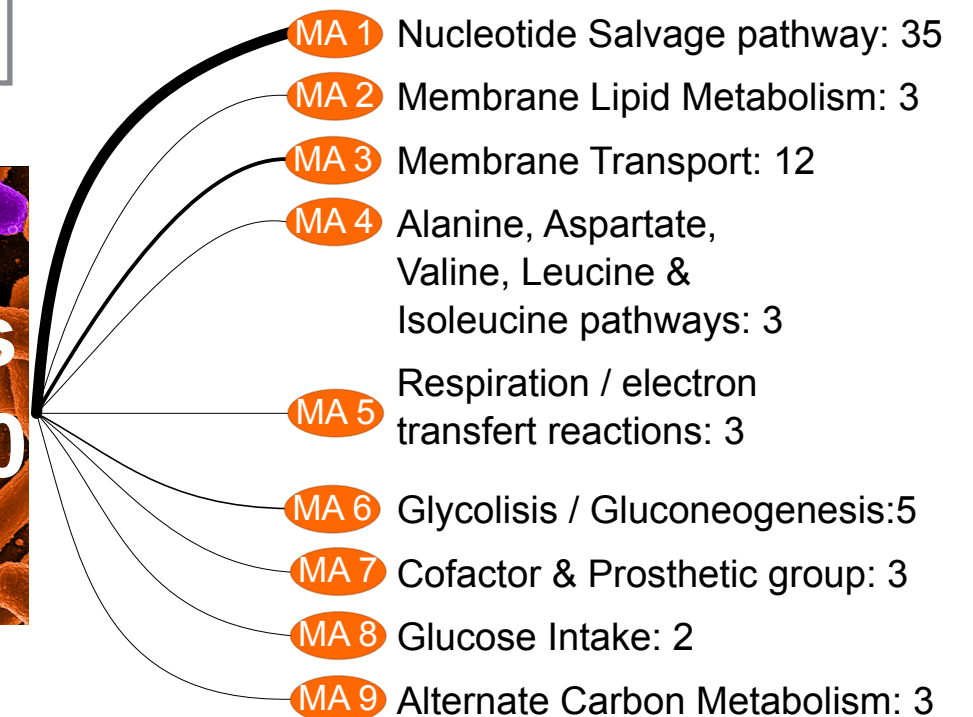
Aerobic Module	Number of Rxns	Anaerobic Module	Number of Rxns	Description
Not in module	2290	Not in module	2312	-
Module MO1	38	Module MA1	35	Nucleotide Salvage Pathways
Module MO2	3	Module MA2	3	Membrane Lipid Metabolism
Module MO3	12	Module MA3	12	Membrane Transport
Module MO4	3	Module MA4	3	Alanine, Aspartate , Valine, Leucine and Isoleucine pathways
Module MO5	14	Module MA5	3	Respiration / Electron transfer reactions
Module MO6	5	Module MA6	5	Glycolysis/ gluconeogenesis
Module MO7	3	Module MA7	3	Cofactor and Prosthetic Group Biosynthesis
Module MO8	11	-	-	Exchange reactions
Module MO9	2	Module MA9	2	Glucose Intake
-	-	Module MA10	3	Alternate Carbon metabolism

MO5 & MA5





***Flux Modules in
Aerobic conditions***

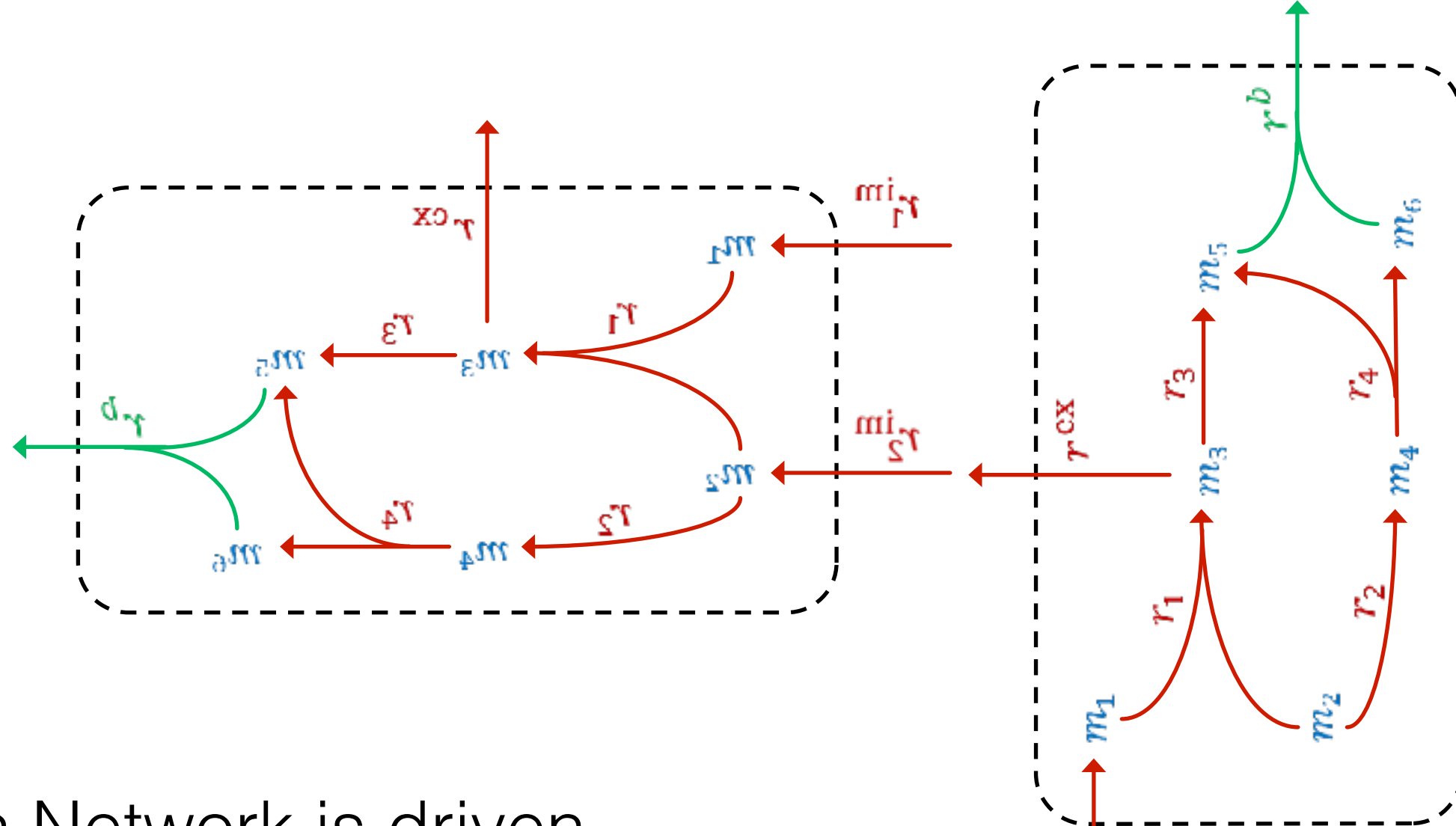


***Flux Modules in
Anaerobic conditions***

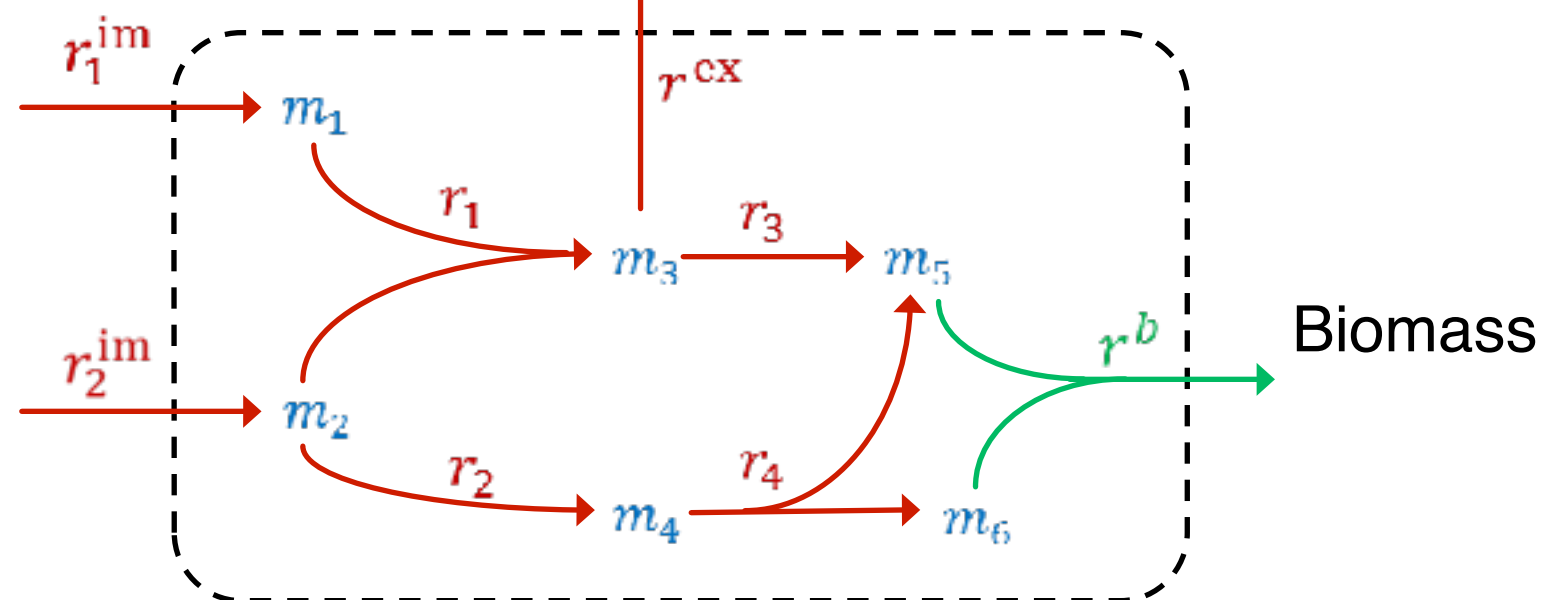
... and so what ?

topics of Marko's PhD

Modeling a microbial community



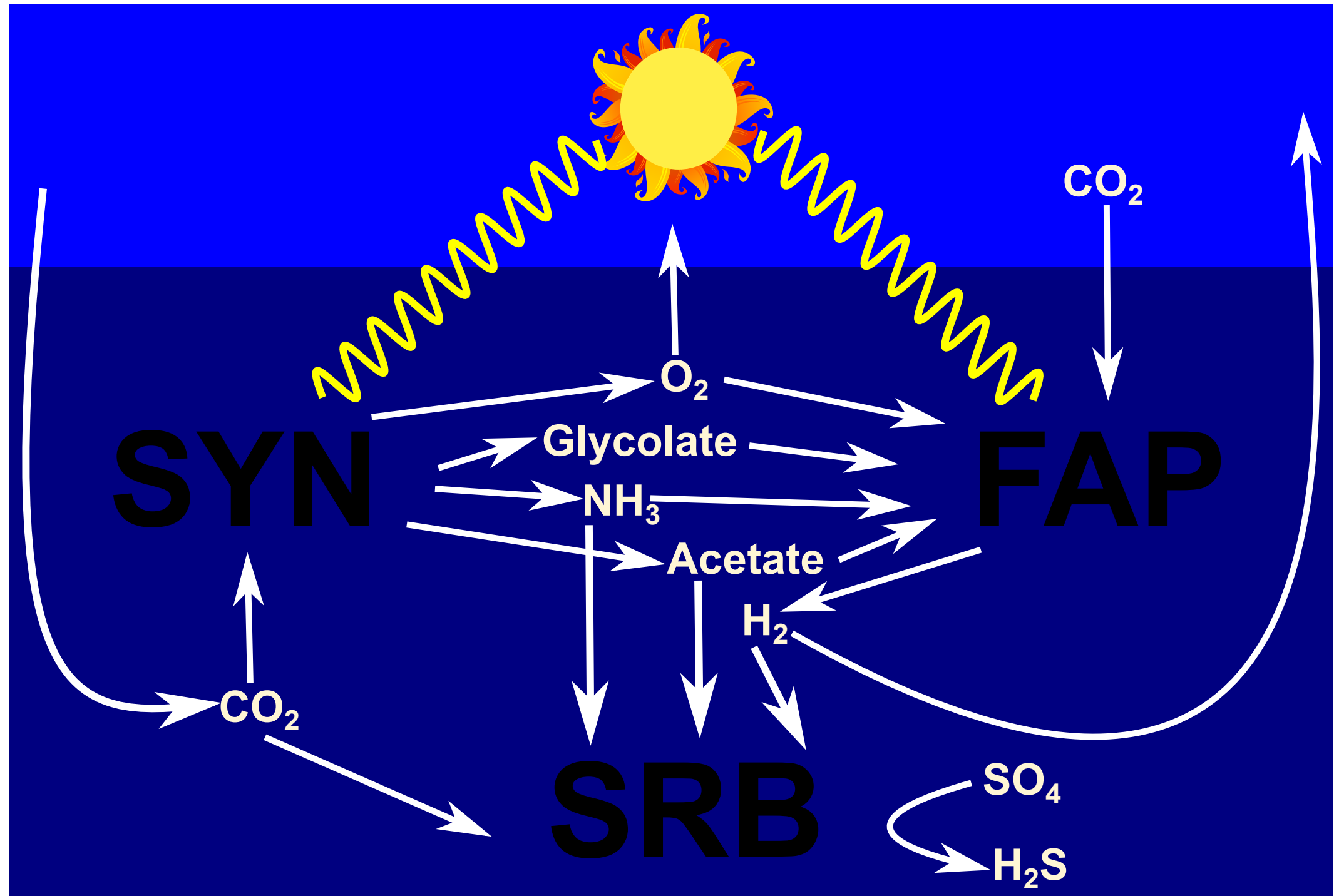
Each Network is driven
by its own objective



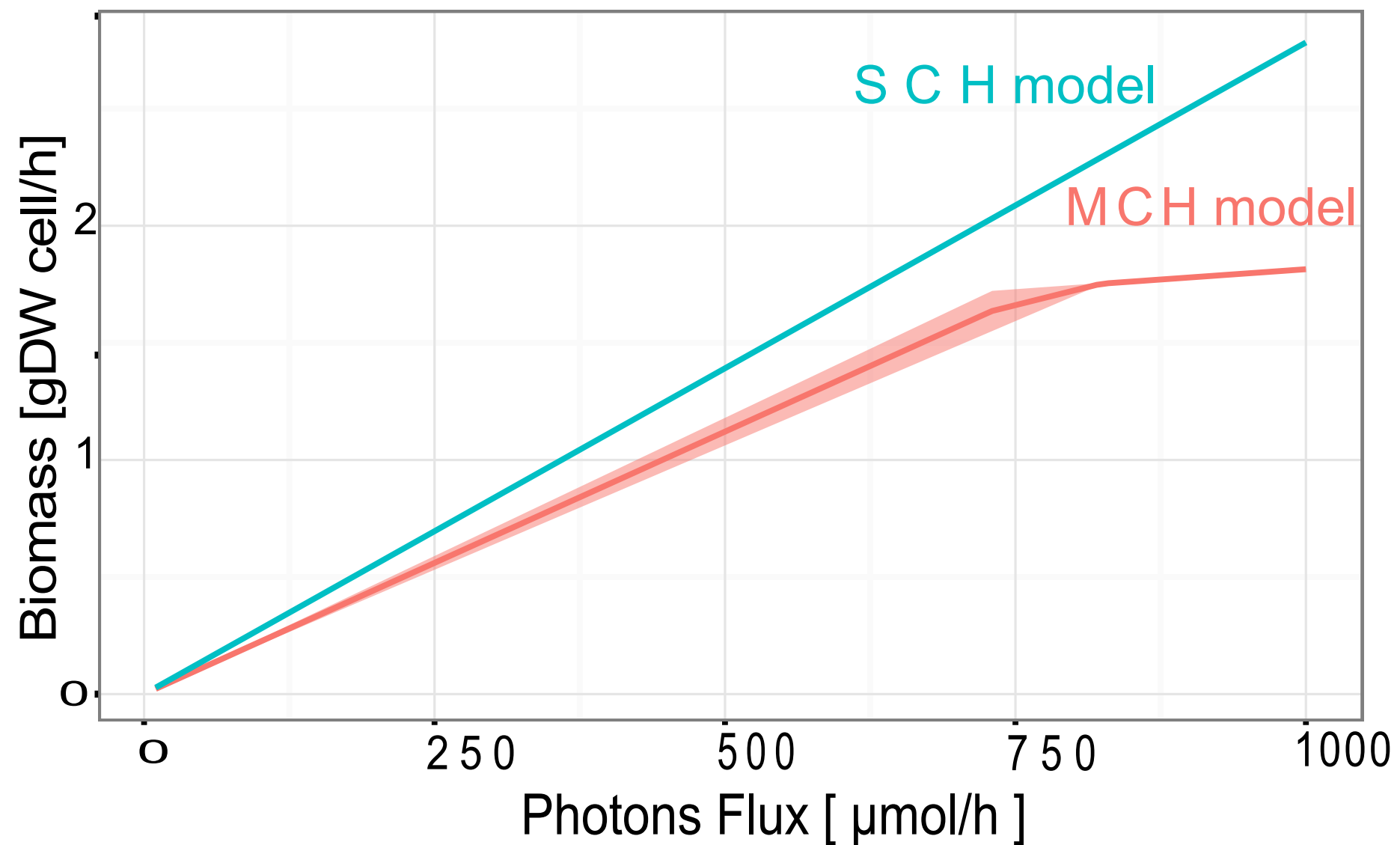
Soup or minestrone ?



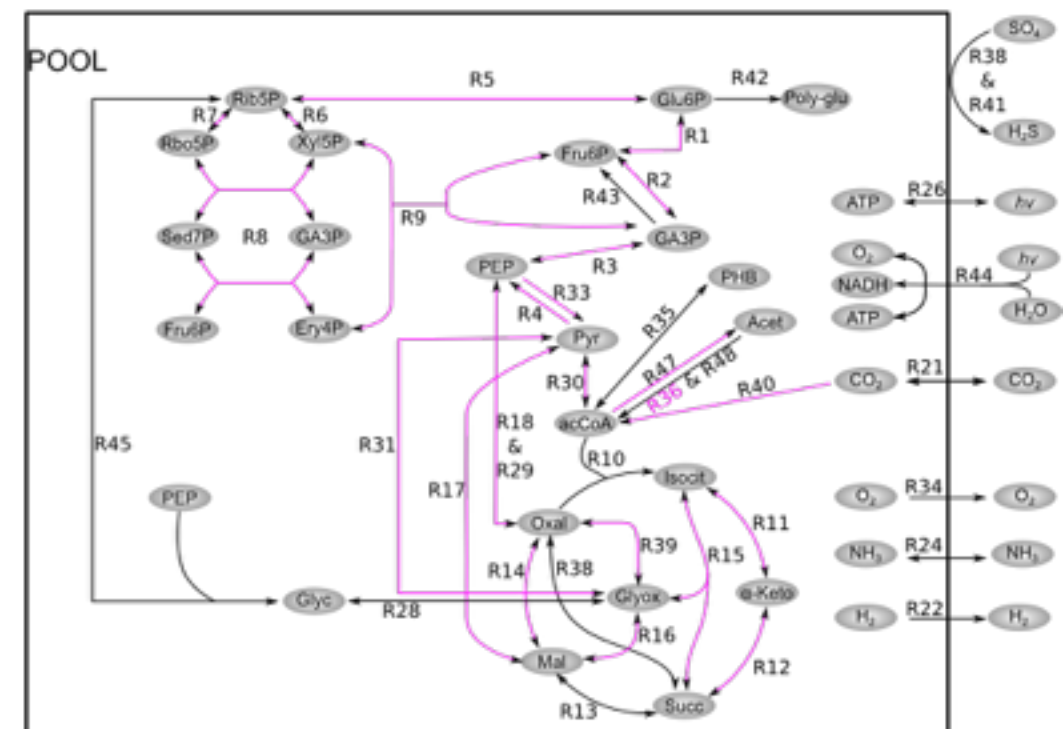
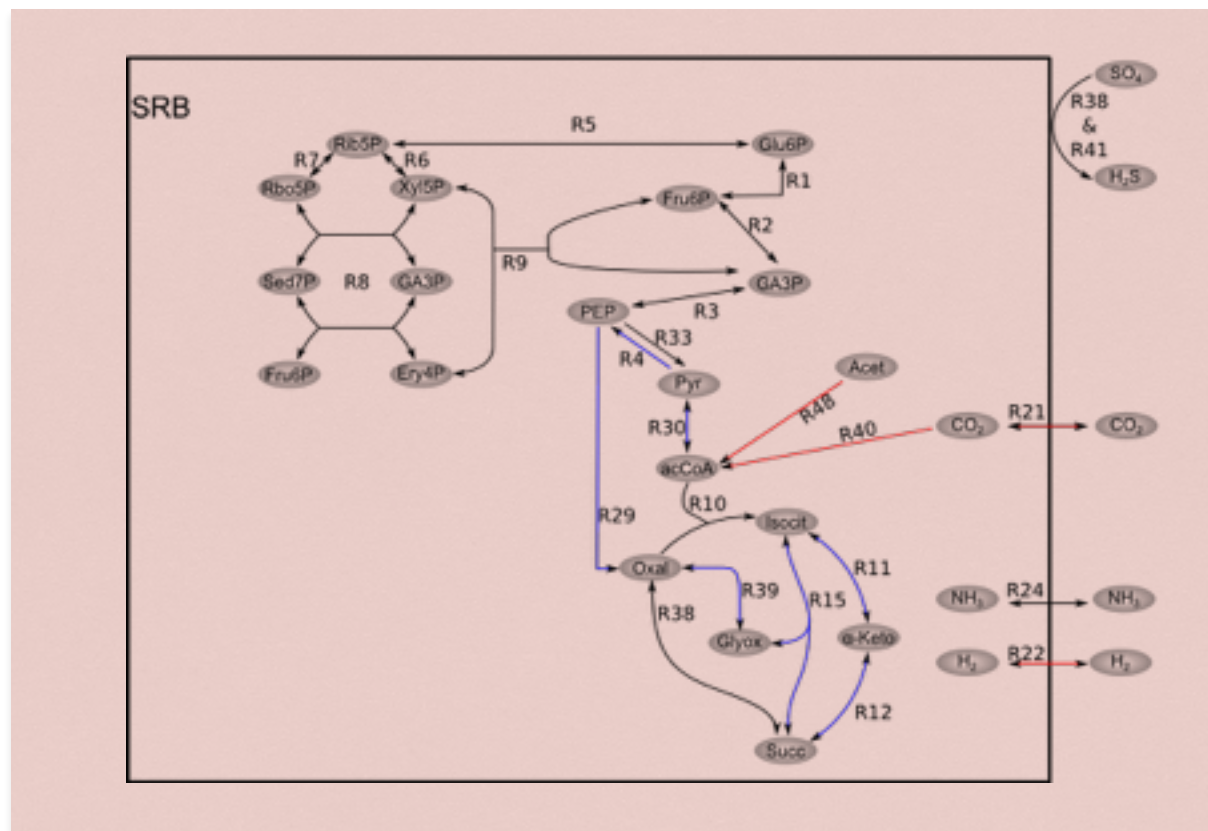
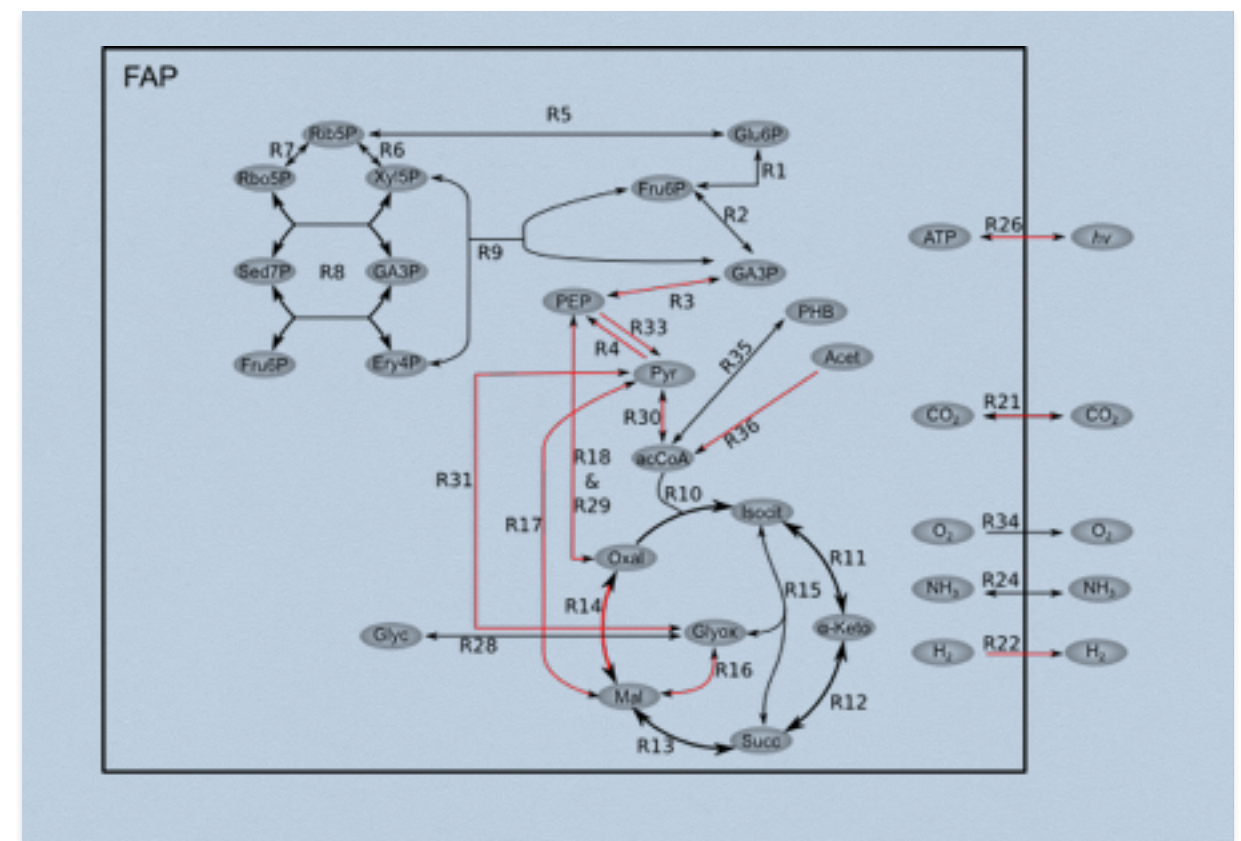
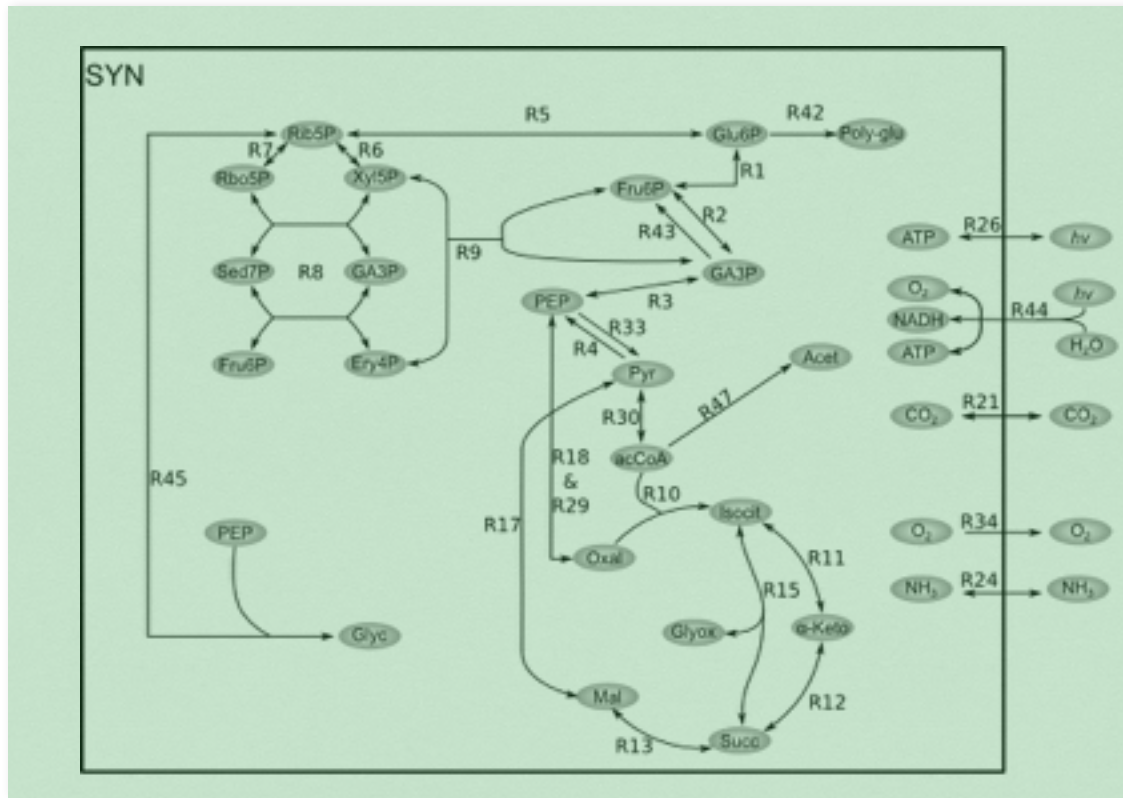
Soup or minestrone ?



Flux Balance ?



Metabolic Modules



Take home message

- Similar quantitative solutions for both assumptions
- BUT different modules :: different optimal solution space
- « Soup » is good for prediction, but « Minestrone » is necessary to understand
- No soup in real life
- Need for a new « multi-objective » paradigm for modeling microbial community

Take Home Messages 2

- Network decomposition based on the Flux Balance paradigm :: very sensitive to the objective
- Reducing the metabolic network by considering modules ?
- Towards a general Methodology:: transient behavior of metabolic network by connecting modules (probabilistic modeling)